REMARKS

Claims 32-77 were pending in the subject application. Claims 32-40 and 43-77 were withdrawn by the Examiner as directed to non-elected inventions. By this amendment, Claims 32-40 and 43-77 have been canceled without disclaimer or prejudice to applicant's right to pursue the subject matter of these claims in a future continuation or divisional application, Claims 41 and 42 have been amended, and new Claims 78-85 have been added. Accordingly, upon entry of this amendment, Claims 41-42 and 78-80 will be pending. Applicant maintains that the amendments do not raise an issue of new matter. Support for the amendments to Claim 41 can be found at least in Claim 36. Support for the amendments to Claim 42 can be found in the previous version of the claim. Support for new Claims 78 and 79 can be found at least in Claim 42. Support for new Claim 80 can be found at least in Claims 36 and 41. Support for new Claims 81-85 can be found at least in Claims 41-42 and 78-80, respectively. Accordingly, entry of the amendment is respectfully requested.

Claim Objection

Claim 41 was objected to as depending on non-elected Claim 36. Reconsideration and withdrawal of this objection are requested in view of the amendments to Claim 41 made herein above.

Rejection under 35 U.S.C. §103(a)

Claims 41 and 42 are rejected as being unpatentable over Dudley et al. (US 2004/0002482), in view of Squelart et al. (Acta Psychiatr. Belg. 77: 284-293, 1977), Medicaments Psychotropics, and Coppen (US 6,191,133).

Applicant respectively traverses this rejection.

The present invention

Before considering the cited art, applicant would like to provide the Examiner with an overview of the present invention.

One of the main problems with contemporaneous psychoactive drugs is their side effects, which limit the usability of these drugs. For instance, the selective serotonin re-uptake inhibitors or SSRIs, which are generally considered to be the first-line antidepressants of choice, block the serotonin transporter responsible for pre-synaptic reuptake. Selective serotonin, nor-adrenaline and dopamine re-uptake inhibitors (SNDRI) and selective serotonin and nor-adrenaline re-uptake inhibitors (SNRI) have this activity in common with SSRIs. Thus, the availability of synaptic serotonin is augmented, leading to a *stimulation* of various 5-HT receptors. However, the simultaneous stimulation of the pre- and postsynaptic serotonin receptors results in several inhibitory effects. Hence, administration of SSRIs causes a negative feedback, which limits the antidepressant actions of these drugs.

The present inventor surprisingly found that the use of a ***daily low dose between 5 - 15 mg*** of pipamperone augments the effect of an SSRI in treating a disease or disorder with an underlying dysregulation of the emotional functionality.

Dose-effect of pipamperone: The inventor surprisingly found that at the claimed daily low dose, pipamperone has a specific, but double effect, *i.e.* a high selective D4 ***and*** 5-HT2A receptor antagonistic effect. As such, pipamperone can exert its augmenting effect on the second, SSRI compound. This effect has not been described in the prior art, nor is there any hint towards such an effect. This daily low dose of pipamperone has ***not*** been used in the prior art.

Pipamperone as a sedative neurolepticum: In the prior art, pipamperone is used at higher doses acting as a ***sedative neurolepticum*** (see e.g. Squelart as well as the manufacturer's instructions, enclosed herewith). As a corollary, the prior art teaches to

use the highest tolerable dose for treating psychoses. However, at these higher doses pipamperone has no therapeutic effect on the SSRI because an antagonistic activity towards the ***D2*** and ***alpha-adrenergic*** receptor takes place, which dominates the clinical effect. This is well-known in the art. This antagonistic activity happens in such a way that negative emerging symptoms like D2 antagonistic related signs as emotional blunting and cognitive problems (the so-called "neuroleptic induced deficit syndrome") and alpha-adrenergic related signs such as dizziness, decreased blood pressure and drowsiness may counteract the symptoms of, but certainly not treat, and least of all, augment the effect of the SSRI in the treated mood or anxiety disorder.

Synergy of low doses pipamperone and selective serotonin receptor inhibitors: Administration of SSRIs has a two-fold effect: the plasma membrane serotonin reuptake transporter is blocked, *i.e.* the effect sought after, and the availability of synaptic serotonin is augmented. The latter effect results in a ***stimulation*** of the 5-HT receptors, which causes several inhibitory effects that limit the actions of these drugs.

The present inventor demonstrated that pipamperone at low doses realizes a highly selective D4 and 5-HT2A receptor antagonistic effect, because of which serotonin resulting from the SSRI cannot bind to the serotonin 2A receptor. As a corollary, the efficacy of the SSRI is increased, but also the cognitive and behavioural problems induced by enhanced D4 stimulation in the meso-cortical cortex as a result of the augmented availability of dopamine via 5-HT2A antagonism is prevented.

Dudley

In essence the Examiner asserts that Dudley discloses the following: combinations for treating or preventing depressive disorders, where the compositions can include pipamperone or citalopram. The Examiner acknowledged that Dudley does not teach both pipamperone and citalopram in the same composition. The Examiner indicated that

the person skilled in the art would be motivated to make such a combination in view of both compounds being described as useful for treating depression; and achieve a synergistic and/or additive effect of the combination.

Dudley relates to subject failing to respond to conventional antidepressants: Applicant notes that Dudley aims at and relates to treating a depressive disorder by administering percutaneously compositions and combinations comprising a steroid in the testosterone synthetic pathway in subjects *failing to respond to conventional antidepressants* and/or who exhibited low or borderline testosterone levels (see paragraph 29). This is illustrated in Example 12, using a testosterone transdermal gel, where it is noted that the subjects were "taking adequate dose of antidepressant medication ... but still complaining of depressive symptoms..." (paragraph 0508).

Dudley teaches an alternative: Dudley provides an alternative for subjects failing to respond to conventional antidepressants, in particular the use of testosterone. The use of testosterone pervades throughout the detailed description. The use of testosterone as the primary compound is explicitly confirmed in paragraphs 119 - 121, 148 - 162, the Examples in general, Examples 1 - 9 (paragraphs 246 - 492) in particular, paragraphs 472-473 relating to mood assessment in response to testosterone alone, the Figures and, first and foremost, the claims. Dudley provides testosterone as an alternative therapy for treating depressive disorders.

Exceptionally, Dudley provides that a further compound may be administered in conjunction with testosterone. Hence, the first compound is always and invariantly testosterone or a steroid in the testosterone synthetic pathway even in a combination of compounds. Paragraph 122 relates to "methods, kits, combinations and compositions" which are used ***in conjunction*** with a pharmaceutical agent, such as an antidepressant. In paragraph 124 "the present invention employs testosterone ***in conjunction*** with a pharmacologically-effective amount of ... an anti-depressant" (emphasis added). The

term "methods, kits, combinations and compositions for treating ...." used in Dudley, always comprises testosterone and possibly a second compound. In paragraphs 131 - 133, the antidepressant agents which can be used ***in conjunction*** with testosterone are exemplified. Although it is mentioned in the last sentence that combinations can be used of the antidepressants, these combinations are to be used ***in conjunction*** with testosterone. Hence, when considering Dudley the person skilled in the art would be taught administering at least testosterone when treating depression. In Claims 81-85 of the instant invention, the pharmaceutical composition consists of the recited components and cannot include testosterone.

Dudley does not teach any combination having a beneficiary effect: Dudley does not disclose any example relating to any combination medication (comprising two non-testosterone compounds) having any effect, even less to a beneficiary effect, even less to a combination comprising two conventional anti-depressants, even less to a combination comprising pipamperone, and least of all a combination comprising pipamperone and citalopram.

It is noted that most examples in Dudley are prophetic, *i.e.* Examples 1-4, 6-9, Example 2 on page 55, and Example 11. Example 5 relates to methods of improving sexual performance and increasing libido in hypogonadal men. Example 10 relates to treatment of hypogonadism in male subjects. Example 12 relates to a method of treating a depressive disorder in a subject. In paragraph 0508 it is noted that "Men age 30-65 years, presently taking an adequate dose of antidepressant medication (as defined by the manufacturer's published product information) for at least the last four weeks, but ***still complaining of depressive symptoms*** sufficient to meet the DSM IV criteria for current major depressive disorder" (emphasis added). Testosterone was added to the antidepressant medication. Neither Pipamperone nor citalopram was used.

Isolating the combination citalopram - pipamperone amounts to undue burden: There is no incentive to combine citalopram with pipamperone. Furthermore, neither of these compounds is a preferred compound (paragraph 133). In paragraph 132, over 140 antidepressants are listed. Each and every combination would encompass about 10^{158} possibilities. Even if only a combination of only two compounds is contemplated (which is denied), about 10,000 possibilities are disclosed. It would amount to undue burden to test each and every combination in order to come to pipamperone and citalopram (in particular considering that the subjects failed to respond to conventional antidepressants). In addition, further to the teachings of Dudley, any combination should be tested with at least three parameters, *i.e.* including testosterone.

Pipamperone is mischaracterized in Dudley: Pipamperone is recommended as a neuroleptic agent but not as an anti-depressant (see for instance the instructions of the manufacturer, enclosed herewith).

Accordingly, applicant maintains that in view of Dudley, the person skilled in the art would:

(i) be taught that classic antidepressants ***do not work*** in a number of cases;

(ii) be taught an alternative for classic antidepressants, *i.e.* testosterone in conjunction with an anti-depressant;

(iii) consider that Dudley fails to provide information that would allow the skilled artisan to practice the instant invention;

(iv) be confronted with undue burden finding a specific combination;

(v) not be motivated to specifically combine citalopram and pipamperone; and

(vi) be confused regarding the characterization of pipamperone as an anti-depressant in view of the manufacturer's instructions.

Squelart and Medicaments Psychotropics

The Examiner indicates that Squelart teaches the use of a neuroleptic drug (pipamperone) for treating chronic schizophrenic patients (80 mg/day) and that Medicaments Psychotropics describes 40mg doses of pipamperone, a neuroleptic. The Examiner also indicated that person skilled in the art would be motivated to combine the teachings of Squelart/Medicaments Psychotropics with Coppen.

Squelart teaches a combination of a neuroleptic and a hypnosedative: Applicant notes that Squelart relates to a study on the usefulness of pipamperone as a sedative neuroleptic drug in troublesome chronic psychotic patients. On page 284, Introduction, Squelart notes that in these "chronic psychotic patients, it is common practice to prescribe a combined treatment consisting of a potent neuroleptic and a hypnosedative one." On page 285, first paragraph it is mentioned that a comparison was made in schizophrenic patients, who were on a maintenance treatment with a combination treatment of incisive neuroleptics and sedative drugs, by replacing the latter ones with pipamperone.

Squelart/Medicaments Psychotropics does not teach the combination of citalopram and pipamperone, even less of any beneficiary effect of this combination.

Squelart/Medicaments Psychotropics teach a dose of at least 40 mg per day: Squelart teaches a combination therapy. However, the dose of pipamperone administered, exceeds the dose of the present set of claims. In particular, at least 40 mg pipamperone was administered per day (see e.g. the note in Table III).

Squelart teaches increasing the dose: Squelart teaches that the "Dosage was gradually ***increased*** from 80 mg/day to an ***optimal level of 160-320 mg/day***" (emphasis added, abstract on page 284).

Accordingly, applicant maintains that in view of Squelart/Medicaments Psychotropics, the person skilled in the art would:

(i) be taught that pipamperone is a sedative neuroleptic drug;

(ii) be taught a combination with neuroleptics;

(iii) be taught a minimal dose of 40 mg per day pipamperone;

(iv) be taught an incentive to increase but not to decrease the daily dose of pipamperone;

(v) be taught an optimal dose of 160-320 mg per day pipamperone; and

(vi) not be taught combining citalopram and pipamperone.

Coppen

The Examiner indicates that Coppen teaches the treatment of depression with citalopram and that the person skilled in the art would be motivated to combine the teachings of Squelart/Medicaments Psychotropics with Coppen.

Coppen teaches a combination of SRI with folate: Applicant maintains that Coppen aims at and relates to treating a depressive disorder by administering compositions and combinations comprising a serotonin reuptake inhibitor (SRI) or a noradrenaline reuptake inhibitor in combination with a folate source in subjects ***failing to respond*** to antidepressants alone (see col.1, ultimate paragraph). There is no incentive to combine an SRI with any other compound, even less with pipamperone.

Coppen teaches normal prescribed dosage rates: Coppen teaches that the SRI and NRI "should be administered in accordance with the ***normal*** prescribed dosage rates". (emphasis added, Column 4, lines 40-42). The "usual daily dose and the standard tablet sizes" (col.4, l.47) are provided in the Table of column 4.

Coppen teaches to increase the dose: If an optimization of the dosage is considered, it is an increase not a decrease. In column 7, lines 57-58 it is mentioned that "[i]f drug dosage has to be ***increased***, the top daily dose is not usually more than 4 times the starting daily dose..." (emphasis added). There is no teaching in Coppen to decrease a dose.

Accordingly, applicant maintains that in view of Coppen, the person skilled in the art would:

(i) be taught that antidepressants ***do not work*** in a number of cases;

(ii) be taught an alternative, *i.e.* folate in conjunction with an anti-depressant;

(iii) be taught to use the usually prescribed dose;

(iv) be taught to increase a dose if the usually prescribed dose does not work; but

(v) not be motivated to combine citalopram and pipamperone.

According to the Examiner, it would be (i) prima facie obvious to combine pipamperone and citalopram and (ii) routine to find the appropriate dose. The reasoning by the Examiner includes presuppositions in order to arrive at the invention. Applicant believes that the teaching of the prior art would never result in the present invention unless applying unallowable hindsight, *i.e.* picking and choosing various elements from the prior art, using these elements out of their context, and making arbitrary combinations to construct an invention in hindsight.

Combination of pipamperone and citalopram. None of the prior art documents explicitly teaches or suggests a combination of pipamperone and citalopram. If such a combination would implicitly have been suggested (which is denied), then it amounts to undue burden to find such a combination (e.g. Dudley). Both Dudley and Coppen advocate the use of a different combination, *i.e.* not using pipamperone with an SSRI, in case the subject fails to respond to the used anti-depressant.

Dudley teaches an alternative for classic antidepressants, *i.e.* testosterone in conjunction with an anti-depressant. Squelart teaches a combination of pipamperone with neuroleptics. Coppen teaches a combination of folate with an anti-depressant.

Please note that the instructions of the manufacturer (enclosed herewith) teach against the combination of pipamperone and citalopram: see "**4.5 Interactions with**

other medicinal products and other forms of interaction -...The simultaneous use of other antipsychotics, lithium, antidepressants, anti-Parkinson medicines and drugs with a central anticholinergic effect increases the risk of the occurrence of tardive dyskinesia." (Emphasis added.)

The instructions of the manufacturer provide the first guiding principle for the diagnosed disorder. Pipamperone has not been recommended and/or approved for use with any of the claimed diseases. Rather, the instructions specify:

"**4.3 Contraindications**- Depression of the central nervous system" (emphasis added).

Furthermore, the instructions specify:

"4.4 Special warnings and precautions for use - ...Major Depression can become visible as a result of antipsychotics. A mood may arise as a result of taking antipsychotics that is difficult to distinguish from depressive symptoms."

"4.8 Undesirable effects

The following side effects may also occur: convulsions, worsening of depressions and dysphoria and malignant neuroleptic syndrome (see special warnings and precautions for use)."

"Other reports concerning the central nervous system

There have been reports of: depression..." (Emphasis added.)

Thus, the instructions of the manufacturer teach against the combination of pipamperone and citalopram.

Finding the appropriate dose. The instruction manual from the manufacturer advises if necessary to increase the starting dose of pipamperone from an initial dose of 40 to 80 mg a day to a maximum of 360 mg per day (see 4.2).

Woggon *et al.* (2000; considered by the Examiner) entitled "Pharmakologische Depressionbehandlung", discusses the difficulties in finding the appropriate dose. On page

83, second column, under the heading "***Wie findet man die richtige Dosis?***", it is stated that:

> "Am besten geht man so vor, daβ man die Dosierung nach einem festen Zeitplan ***so rasch wie möglich steigert***, daβ entweder eine Wirkung sichtbar wird oder bis sich zeigt , daβ das Präparat nicht vertragen wird." (emphasis added).
>
> "It is recommended that the dose is increased ***as fast as possible***, according to a set time schedule, such that either the effectiveness or the side-effects are observed."

Squelart teaches that the "Dosage was gradually ***increased*** from 80 mg/day to an ***optimal level of 160-320 mg/day***" (emphasis added, abstract on page 284).

In column 7, lines 57-58 Coppen mentions that "if drug dosage has to be ***increased***, the top daily dose is not usually more than 4 times the starting daily dose..." (emphasis added).

Thus, the teaching is ***unidirectional***, *i.e.* to increase a dose. In case the medication is not tolerated, a different medicament is prescribed. There is no incentive to lower a dose.

Routine experimentation: Finding an appropriate dose presupposes a correct diagnosis of the disorder. In the present case, pipamperone is not recommended for the claimed disorders.

There is no teaching of lowering a dose. The art points towards one direction: using the highest tolerable dose. Hence, routine experimentation would be increasing a dose, and observing whether an effect is realized.

Moreover, in the present case, the enhanced clinical effect is dependent upon two compounds, which act synergistically. However, at other doses, these compounds have no

mutual effect, or even have opposing effects. This adds to the complexity of determining any dose.

Thus, determining at which dose pipamperone augments the efficacy of a second compound is certainly not routine, but either goes against the teaching in the art or amounts to undue burden.

No incentive to lower the dose of pipamperone: From the art and standard textbooks it can be learned that pipamperone is used as a sedative neurolepticum at a dose of 40 mg/day and higher (see for instance the instructions of the manufacturer, and Squelart). Specifically, it is known that the high dose pipamperone results in D2 receptor related dopaminergic and H1 receptor related histaminergic antagonism, which is responsible for the neuroleptic-sedative effect. This antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day. Accordingly, there would be no incentive to decrease the amount of pipamperone administered, since this would lower the neuroleptic-sedative effect.

Combination of Dudley - Squelart - Coppen

Applicant believes that none of the cited documents as such teaches or suggests the invention for reasons set out above.

Secondly, it is submitted that the person skilled in the art has no motivation to combine these three documents, not even with unallowable hindsight. Although both Dudley and Coppen relate to the problem of classic antidepressants which ***do not work*** in a number of cases, each document provides a completely different solution. Dudley teaches to combine testosterone in conjunction with an anti-depressant. Coppen teaches to combine folate with an anti-depressant. There is no incentive to combine folate and testosterone. Squelart teaches that pipamperone is a sedative neuroleptic drug, but not an anti-depressant.

Third, even if it is assumed for the sake of discussion that these documents are combined by the person skilled in the art (which is denied), then there appear insurmountable gaps in the combined teachings. Specifically, there is no specific teaching to use pipamperone with citalopram. There is no guidance whatsoever on the dose of pipamperone. In fact, Squelart teaches away from the claimed dose. There is no teaching that pipamperone would have an effect on an SSRI, even less that the effect of the SSRI can be increased by this low dose of pipamperone.

Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached form PTO/SB/08A-B (2 pages).

Applicant notes that the Examiner has returned previously submitted PTO/SB/08A-B forms, which have been initialed to indicate that the listed documents have been considered by the Examiner. With the current Office Action, applicant received two copies of PTO/SB/08B submitted with an IDS dated August 10, 2007. However, applicant has yet to receive a returned copy of the PTO/SB/08A form submitted with the August 10, 2007 IDS. Accordingly, enclosed herewith is a replacement of the PTO/SB/08A form submitted with the August 10, 2007 IDS. The Examiner is requested to initial and return the form to applicant.

CONCLUSIONS

In view of the remarks and amendments made hereinabove, reconsideration and withdrawal of the rejections and objections set forth in the January 23, 2008 Office Action and passage of the pending claims to allowance are respectfully requested. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $180.00 is enclosed for the fee for filing an Information Disclosure Statement. No additional fee is deemed necessary in connection with the filing of this response. However, if any other fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: April 23, 2008
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By _____
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